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TITLE: Effect of Teriparatide, Vibration, and the Combination on Bone Mass and Bone Architecture in Chronic Spinal Cord Injury

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14. ABSTRACT Severe bone loss commonly occurs in individuals with chronic spinal cord injury who are non-weightbearing and leads to an increased risk of lower extremity fractures. This 12 month , multi-site, double-blind, randomized, placebo-controlled study evaluates the efficacy and safety of two interventions known to be anabolic to bone, parathyroid hormone and mechanical loading (Provided as teriparatide and vibration, respectively) in 60 SCI individuals with low bone mass. At the end of the second year of this project, 80 participants have been screened and 28 enrolled with 6 currently in the run-in phase. Disposition of the 28 subjects enrolled includes 3 participants who have completed the study. 24 Active and 1 who has Discontinued. No safety issues have arisen during the study. Results regarding efficacy will only be available at the completion of the trial.					
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INTRODUCTION:

After acute spinal cord injury (SCI), individuals unable to ambulate experience rapid and profound bone loss of as much as 50% in their lower extremities over the ensuing 2-5 years. This bone loss results in their having a significantly increased risk of fracture thereafter. This study evaluates the ability of two interventions, parathyroid hormone and mechanical loading, separately and together, to increase bone mass and improve bone quality in individuals with chronic SCI and low bone mass. These interventions have previously been shown to be effective in increasing bone mass and decreasing fractures in non-disabled populations of men and post-menopausal women but not examined in individuals with SCI. In this three-arm, modified factorial design, double-blind, placebo-controlled study, 60 people with chronic SCI will receive daily teriparatide and mechanical vibration. Assessment of bone mass (by DXA scanning and quantitative computed tomography), bone quality (by finite element modeling), and bone metabolism (by serum bone markers) will be undertaken at baseline and at regular intervals during one year of treatment to permit evaluation of the efficacy of these interventions.

BODY:

Overview of Yr 2 Progress:

During the second year of this program, the focus has been on recruitment of participants and collection of data. Both of the clinical sites are active. The Northwestern/RIC site screened 48 participants during year 2, enrolled 22 with an additional 4 in the run-in phase. A total of 27 participants have been enrolled at this site to date. The Hines VA site has obtained IRB approval during year 2 and enrolled 1 participant with 3 in the run-in phase. Therefore, a total of 28 participants have been enrolled; 24 are currently active, 3 have completed the trial, and only 1 has discontinued or been lost to follow up. Adherence has been excellent. Treatment has been well tolerated and no unexpected safety issues have been identified thus far. The Medical Monitor has reviewed the study at 2 regularly-scheduled meetings and recommended continuation. Because the screen failure rate continued to be high and surprisingly excluded many individuals with extremity fracture, the protocol was amended at the end of year 2 to allow inclusion of people with SCI and extremity fracture who had a bone mineral density T-score measurement at the hip of -2.0 or lower rather than -2.5. An IND application was submitted to the FDA based on this change and the amended protocol approved at both study sites. The database for collection of study data has been finalized and data are being entered. All DXA scan and CT data have been analyzed and are current.

Research Accomplishments:

The following items are listed in the statement of work (SOW) for Yr 2 and Yr 3 of the project.

1. Identify and recruit participants: planned enrollment rate is 3 participants/month; 2 participants/month from Northwestern/RIC and 1 participant/month from Edward Hines, Jr VA Hospital
2. Perform all study visits, assessments and procedures as outlined in the protocol
3. Continuous collect and monitor safety data with reporting as needed to the IRB, Medical Monitor and HRPO
4. Collect, verify and enter all data into the database
5. Obtain serum samples and store for batch analysis at the end of the study
6. Collect all DXA data and enter into database

7. Acquire all CT data and transmit to UIC for analysis
8. Meet every 6 months with Medical Monitor to review safety reports
9. Complete annual report to IRB and regulatory authorities

As detailed in last year's progress report, the SOW was amended with DOD approval to add a second study site, Edward Hines, Jr VA Medical Center a designated VA center of excellence in spinal cord injury. It was anticipated that they would enroll 1 participant/month and the Northwestern/RIC site would therefore enroll 2 participants/month. Additionally, because MicroMRI was no longer in business, CT technology with equivalent sensitivity was introduced with the addition of collaborators at the University of Illinois at Chicago (UIC) who perform the analyses of these data. These changes are reflected in the above SOW.

All of the above tasks have been initiated successfully and are on-going as anticipated with the exception of the rate of enrollment at the Hines VA site.

1. At the Northwestern/RIC site, 22 participants have been enrolled during year 2, with 3 currently in the run-in phase. This represents an enrollment rate of 1.83 participants/month and is 2 shy of the projected number planned for the year. At the Hines VA site, only 1 participant has been enrolled, despite pre-screening a very large number of potential participants. The failure to enroll subjects was found to be due to the difficulty and/or unwillingness of VA participants to travel to the imaging site at Northwestern/RIC. To overcome this issue, arrangements were made for imaging to be done at Hines VA. Regulatory approval by Hines VA has recently been approved. 10 participants have been consented and 3 are currently in the run-in phase; it is hoped that an accelerated recruitment can be achieved in the coming year at this site.
2. Protocol adherence has been excellent. Only 1 participant who had been entered into the study is no longer being followed (retention rate of 96.4%).
3. Because a significant number of SCI individuals presented with a history of extremity fracture and had low hip BMD but did not meet the WHO criteria for osteoporosis (developed for post-menopausal women), it was felt desirable to include such people in this study as they would be a prime population for need and use of this type of intervention. Therefore, the study protocol was amended to permit enrollment of people with SCI who had experienced extremity fractures, demonstrating loss of bone strength, with BMD values that were in the osteopenic (T-score ≤ -2.0) rather than osteoporotic (T-score ≤ -2.5) range. An IND application was submitted to the FDA, and IRB approval has been obtained at all study sites. HRPO review is currently underway prior to implementation.
4. All adverse event data are being systematically collected. No unanticipated serious adverse events related to the study interventions (drug or device) have been reported at this time.
5. The research database has been finalized and data are being entered. A double-data entry system is being employed to assure high data accuracy.
6. Serum samples have been collected on all participants and are being stored for batch analysis at study conclusion.
7. All DXA data have been analyzed and are being entered into the study database.

8. CT data have all been transferred to UIC for analysis. Analysis of these data is currently up to date.
9. Meetings with medical monitor have occurred as scheduled. The recommendation from the Medical Monitor has been to continue the study in its current form. No safety issues have been identified.
10. All annual and regulatory reports have been filed and accepted.

KEY RESEARCH ACCOMPLISHMENTS:

There are no outcome data available to date. As this is a blinded clinical trial, scientific data relating to study objectives will not be available until all participants have concluded the study, data cleaned and data base locked, and analyses completed.

REPORTABLE OUTCOMES:

The project remains in the phase of data collection. Approximately half of the participants have provided baseline data; no data are available of the effects of the interventions being assessed as we remain blinded until completion of data collection.

CONCLUSION:

This project has not progressed to the point of being able to provide any conclusions in regard to the effect of these specific interventions on bone mass or bone quality in people with spinal cord injury. Enrollment is on target to permit completion of enrollment at some point during the second half of year 3. Data analysis can then be initiated at the end of year 4.

REFERENCES:

None.

APPENDICES:

None.

SUPPORTING DATA:

Baseline Data of Enrolled Participants

Demographic Data

Mean Age (yr, SD))	41.5 ± 14.4
Sex	22M/6F
Ethnicity	21 Not Hispanic or Latino, 7 Hispanic or Latino
Race	15 Black, 13 White
BMI	24.3 ± 5.0

Clinical Descriptors

Time post-SCI (yr, SD)	16.0±12.1
Injury Level (cervical/thoracic)	8 C/20 Th
Motor Complete/Incomplete	11 Complete/17 Incomplete

Baseline BMD Values (SD)

Spine BMD	0.991 ± 0.15
R Total Hip	0.659 ± 0.11
R Femoral Neck	0.657 ± 0.12
L Total Hip	0.630 ± 0.15
L Femoral Neck	0.637 ± 0.17

Study Status

Enrolled			
	NU	VA	Total
Signed ICF	70	10	80
Screen Failure	40	6	46
Run In	3	3	6
Randomized	27	1	28
Week 2	23	1	24
Week 6	19	1	20
Month 3	18	1	19
Month 6	8	0	8
Month 9	6	0	6
Month 12/Completed	3	0	3
Lost to Follow up	1	0	1